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(54) Title: CHIMERIC LEPTIN FUSED TO IMMUNOGLOBULIN DOMAIN AND USE

(57) Abstract

Chimeric leptin which are proteins comprising leptin or a mutant or a variant thereof fused to a human immunogobulin domain. One favoured immunoglobulin domain is the human immunoglobulin Fc domain. The chimeric derivatives of leptin have, despite their large molecular size, good pharmacological activity combined with prolonged clearance rates. These derivatives of leptin are therefore indicated to be particularly useful for the treatment or prophylaxis of obesity or diseases and conditions associated with obesity such as atherosclerosis, hypertension and type II diabetes.

CHIMERIC LEPTIN FUSED TO IMMUNOGLOBULIN DOMAIN AND USE

The present invention relates to a novel compound being a novel chimeric protein, to a process for the preparation of such a compound, a pharmaceutical composition comprising such a compound and the use of such a compound in medicine, especially for the treatment of obesity and associated diseases.

European Patent Application, Publication number 0 464 533 discloses fusion proteins comprising various portions of the constant region of immunoglobulin molecules together with another human protein or part thereof. European Patent Application, Publication number 0 297 882 discloses fusion proteins comprising various portions of the plasminogen molecule with part of another human protein.

Zhang et al. (Nature: 372, 425 - 432; 1994) describe the positional cloning of a mouse obese gene and its human homologue. The sequence of the Open Reading Frame (ORF) of the mouse gene predicts a polypeptide of 167 amino acids and Zhang et al. predicted the presence of a signal sequence which would lead to the production of a mature protein of 146 residues. The human homologue was disclosed as having a similar size of 146 amino acids for the mature protein. Zhang et al. showed the presence of a primary translation product of approximate size of 18 kilodaltons (kD) with truncation to a 16kD product on addition of microsomal membranes, consistent with the production of a pre-protein and the removal of an N-terminal signal sequence. Zhang et al also disclose the potential use of the human obese gene product (hereinafter 'leptin') in the treatment of obesity.

For effective, practical treatment of obesity a particularly desirable property of an obesity agent is a clearance rate in humans commensurate with patient acceptable treatment regimens, especially regimens for injectable therapies. Zhang et al. do not disclose information relating to the clearance rate of the active molecule in either mouse or humans.

The precise mechanism of action of leptin is currently unknown, however it is considered that in order to provide the observed pharmacological effects, leptin must interact with one or more receptors in the brain.

We have now discovered certain chimeric derivatives of leptin which surprisingly, despite their large molecular size, have good pharmacological activity combined with prolonged clearance rates. These chimeric derivatives of leptin are therefore indicated to be particularly useful for the treatment or prophylaxis of obesity and for the treatment or prophylaxis of diseases and conditions associated with obesity, such as atherosclerosis, hypertension and, especially, Type II diabetes. In particular these compounds are considered to be useful for administration by injection.

component suitably comprises the CH2 and CH3 domains and the hinge region including cysteine residues contributing to inter-heavy chain disulphide bonding.

For example when the IgG component is derived from IgG4 it includes cysteine residues 8 and 11 of the IgG4 hinge region (Pinck J.R. and Milstein C., Nature vol216pp941-942, 1967). Preferably the IgG4 component consists of amino acids corresponding to residues 1-12 of the hinge, 1-110 of CH2 and 1-107 of CH3 of IgG4 described by Ellison J., Buxbaum J. and Hood L., DNA vol1pp11-18, 1981. In one example of a suitable mutation in IgG4, residue 10 of the hinge (residue 241, Kabat numbering) is altered from serine (S) in the wild type to proline (P) and residue 5 of CH2 (residue 248, Kabat numbering) is altered from leucine (L) in the wild type to glutamate (E).

DNA polymers which encode mutants or variants of the human immunoglobulin may be prepared by site-directed mutagenesis of the cDNA which codes for the required protein by conventional methods such as those described by G. Winter *et al* in Nature 1982, **299**, 756-758 or by Zoller and Smith 1982; Nucl. Acids Res., **10**, 6487-6500, or deletion mutagenesis such as described by Chan and Smith in Nucl. Acids Res., 1984, **12**, 2407-2419 or by G. Winter *et al* in Biochem. Soc. Trans., 1984; **12**, 224-225 or polymerase chain reaction such as described by Mikaelian and Sergeant in Nucleic Acids Research, 1992, **20**, 376.

When used herein 'compound of the invention' or 'compounds of the invention' relates to the above mentioned chimera.

In a further aspect, the invention provides a process for preparing a compound according to the invention which process comprises expressing DNA encoding said compound in a recombinant host cell and recovering the product.

The DNA polymer comprising a nucleotide sequence that encodes the compound also forms part of the invention.

The process of the invention may be performed by conventional recombinant techniques such as described in Maniatis *et. al.*, Molecular Cloning - A Laboratory Manual; Cold Spring Harbor, 1982 and DNA Cloning vols I, II and III (D.M. Glover ed., IRL Press Ltd).

In particular, the process may comprise the steps of:

i) preparing a replicable expression vector capable, in a host cell, of expressing a DNA polymer comprising a nucleotide sequence that encodes said compound;

ii) transforming a host cell with said vector;

iii) culturing said transformed host cell under conditions permitting expression of said DNA polymer to produce said compound; and

iv) recovering said compound.

molecule encoding a said leptin or variant and a second DNA molecule encoding a said immunoglobulin domain or fragment thereof.

The DNA molecules may be obtained by the digestion with suitable restriction enzymes of vectors carrying the required coding sequences or by use of polymerase chain reaction technology.

The precise structure of the DNA molecules and the way in which they are obtained depends upon the structure of the desired product. The design of a suitable strategy for the construction of the DNA molecule coding for the compound is a routine matter for the skilled worker in the art.

The expression of the DNA polymer encoding the compound in a recombinant host cell may be carried out by means of a replicable expression vector capable, in the host cell, of expressing the DNA polymer. The expression vector is novel and also forms part of the invention.

The replicable expression vector may be prepared in accordance with the invention, by cleaving a vector compatible with the host cell to provide a linear DNA segment having an intact replicon, and combining said linear segment with one or more DNA molecules which, together with said linear segment, encode the compound, under ligating conditions.

The ligation of the linear segment and more than one DNA molecule may be carried out simultaneously or sequentially as desired.

Thus, the DNA polymer may be preformed or formed during the construction of the vector, as desired.

The choice of vector will be determined in part by the host cell, which may be prokaryotic, such as *E. coli*, or eukaryotic, such as mouse C127, mouse myeloma, chinese hamster ovary, Cos1 or Hela cells, fungi e.g. filamentous fungi or unicellular yeast or an insect cell such as Drosophila. The host cell may also be a transgenic animal.

A preferred host cell is Cos1.

Suitable vectors include plasmids, bacteriophages, cosmids and recombinant viruses derived from, for example, baculoviruses, vaccinia or Semliki Forest virus.

The preparation of the replicable expression vector may be carried out conventionally with appropriate enzymes for restriction, polymerisation and ligation of the DNA, by procedures described in, for example, Maniatis et al., cited above. Polymerisation and ligation may be performed as described above for the preparation of the DNA polymer. Digestion with restriction enzymes may be performed in an appropriate buffer at a temperature of 20°-70°C, generally in a volume of 50µl or less with 0.1-10µg DNA.

in metabolic rate or oxygen consumption. Multiple injections of the active compound - at most twice daily - over a period of a week for rodents or a month for primates, also cause a reduction in body weight and in the size of discrete adipose tissue depots.

Clearance rates are determined by conventional plasma assay using ob-antibodies, for example ELISA methodology.

As indicated above the compounds of the present invention have useful pharmaceutical properties, in particular anti obesity activity and also for the treatment of diseases associated with obesity, such as atherosclerosis, hypertension and, especially, Type II diabetes.

In use the compound will normally be employed in the form of a pharmaceutical composition in association with a human pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will depend on the mode of administration.

The active compound may be formulated for administration by any suitable route and is preferably in unit dosage form. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

The invention therefore further provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier.

The dosage ranges for administration of the compounds of the present invention are those to produce the desired therapeutic effect. Dosage will generally vary with age, extent or severity of the medical condition and contraindications, if any. For example in the treatment of obsity the unit dosage can vary from less than 1mg to 300mg, but typically will be in the region of 1 to 20mg per dose, in one or more doses, such as one to six doses per day, such that the daily dosage is in the range 0.02-40mg/kg.

Dosages and compositions for the treatment of diseases associated with obesity such as atherosclerosis, hypertension and, especially, Type II diabetes are selected from an equivalent range to that used in the treatment of obesity.

Compositions suitable for injection may be in the form of solutions, suspensions or emulsions, or dry powders which are dissolved or suspended in a suitable vehicle prior to use.

Fluid unit dosage forms are prepared utilising the compound and a pyrogen-free sterile vehicle. The compound, depending on the vehicle and concentration used, can be

The invention also provides the use of a compound of the invention in the manufacture of a medicament for treating obesity or diseases associated with obesity, such as atherosclerosis, hypertension and, especially, Type II diabetes.

As indicated above the invention also encompasses cosmetic treatments.

Accordingly, there is also provided a compound of the invention for use in the cosmetic treatment of human or non-human mammals.

There is also provided a method for the cosmetic treatment of a human or non-human mammal, which treatment comprises administering an effective, non-toxic amount of a compound of the invention to a human or non-human mammal in need thereof.

Cosmetic treatment suitably includes treatment for the improvement of body appearence, such as weight reduction treatment.

The invention also extends to a cosmetic composition, comprising a compound of the invention and a carrier therefor.

Compositions of the invention including cosmetic compositions are formulated using known methods, for example those described in standard text books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, the British and US Pharmacopoeias.

No unexpected toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The following Examples illustrate the invention but do not limit it in any way.

CCTGAATTTCTGGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTC
600

ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCC
660

GAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCG
720

CGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
780

GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCATCG
840

ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTG
900

CCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
960

TTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTAC
1020

AAGACCACGCCTCCCGTGCTGGACTCCGACGGATCCTTCTTCCTCTACAGCAGGCTAACC
1080

GTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCT
1140

CTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAA
1188

Table 2. Amino acid sequence of leptin/IgG4 chimera, 396aa

1 MHWGTLCGFL WLWPYLFYVQ AVPIQKVQDD TKTLIKTIVT RINDISHTQS

51 VSSKQKVTGL DFIPGLHPIL TLSKMDQTLA VYQQILTSMP SRNVIQISND

101 LENLRDLLHV LAFSKSCHLP WASGLETLDS LGGVLEASGY STEVVALSRL

151 QGSLQDMLWQ LDLSPGCESK YGPPCPSCPA PEFLGGPSVF LFPPKPKDTL

201 MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR

Example 2.

Construction of DNA coding for fusion protein ob 1-167/IgG4 hinge-CH2-CH3 PE variant

The gene coding for a fusion protein comprising the human 'ob' protein and the Hinge-CH2-CH3 region of human IgG4 PE (a form of IgG4 mutated as below) is created by recombinant DNA technology, preferably by a two-step recombinant PCR method.

The cDNA coding for the complete human leptin, amino acids 1-167(numbering as Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold & J. Friedman. Nature 372: 425-432) is joined at the 3' end to the 5' end of the hinge-CH2-CH3 region of the cDNA coding for the human IgG4 (PE variant) protein, shown as amino acids 168-396 in the protein sequence below.

The human 'ob' gene has been prepared synthetically based on the amino acid sequence of Zhang et al, and assembled in the pcDNA3 vector. The encoded protein sequence is given in Table 2.

Human IgG4 heavy chain PE variant. In IgG4 PE, residue 10 of the hinge (residue 241, Kabat numbering) is altered from serine (S) in the wild type to proline (P) and residue 5 of CH2 (residue 248, Kabat numbering) is altered from leucine (L) in the wild type to glutamate (E). Angal S., King D.J., Bodmer M.W., Turner A., Lawson A.D.G., Roberts G., Pedley B. and Adair R., Molecular Immunology vol30pp105-108, 1993, describe an IgG4 molecule where residue 241 (Kabat numbering) is altered from serine to proline. This change increases the serum half-life of the IgG4 molecule.

The IgG4 PE variant was created using PCR mutagenesis on the synthetic human IgG4 heavy chain cDNA. The sequence of the IgG4 PE variant is described in Table 1. The residues of the IgG4 nucleotide sequence which were altered to make the PE variant are as follows:

referring to Table 1:

residue 322 has been altered to "C" in the PE variant from "T" in the wild type;

residue 333 has been altered to "G" in the PE variant from "A" in the wild type; and

residues 343-344 have been altered to "GA" in the PE variant from "CT" in the wild type.

The fusion protein was expressed transiently in Cos1 cells using the pCDN vector system, as described in International Patent Application Publication number WO 96/04388. The mature protein was exported from the cells into the culture medium and was detected by anti-leptin antibody. It was shown to to have a size consistent with the predicted structure by Western blotting analysis under both reducing and nonreducing conditions.

CTGGAGAACCTCCGGGATCTTCTTCACGTGCTGGCCTTCTCTAAGAGCTGCCACTTGCCC
360
TGGGCCAGTGGCCTGGAGACCTTGGACAGCCTGGGGGGTGTCCTCGAGGCTTCAGGCTAC
420
TCCACAGAGGTGGTGGCCCTGAGCAGGCTGCAGGGGTCTCTGCAGGACATGCTGTGGCAG
480
CTGGACCTCAGCCCCGGGTGCGAGTCCAAATATGGTCCCCCATGCCCAcCATGCCCAGCg
540
CCTGAATTTGAGGGGGGACCATCAGTCTTCCTGTTCCCCCCAAAACCCAAGGACACTCTC
600
ATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCAGGAAGACCCC
660
GAGGTCCAGTTCAACTGGTACGTGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCG
720
CGGGAGGAGCAGTTCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAG
780
GACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCATCG
840
ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTG
900
CCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGC
960
TTCTACCCCAGCGACATCGCCGTGGAGTTGGAGAGCAATGGGCAGCCGGAGAACAACTAC
1020
AAGACCACGCCTCCCGTGCTGGACTCCGACGGATCCTTCTTCCTCTACAGCAGGCTAACC
1080
GTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCT
1140
CTGCACAACCACTACACACAGAAGAGCCTCTCCCTGTCTCTGGGTAAA
1188

Table 4: Amino acid sequence of ob 1-167/IgG4 hinge-CH2-CH3 PE variant chimera 396aa

SEQ ID No: 2

1 MHWGTLCGFL WLWPYLFYVQ AVPIQKVQDD TKTLIKTIVT RINDISHTQS

51 VSSKQKVTGL DFIPGLHPIL TLSKMDQTLA VYQQILTSMP SRNVIQISND

101 LENLRDLLHV LAFSKSCHLP WASGLETLDS LGGVLEASGY STEVVALSRL

151 QGSLQDMLWQ LDLSPGCESK YGPPCPPCPA PEFEGGPSVF LFPPKPKDTL

201 MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR

251 VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL

301 PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD

The mature protein was exported from the cells into the culture medium and was detected by anti-leptin antibody. It was shown to to have a size consistent with the predicted structure by Western blotting analysis under both reducing and nonreducing conditions.

Table 5. DNA sequence of ob/IgG1 chimera 1197bp

ATGCATTGGGGAACCCTGTGCGGATTCTTGTGGCTTTGGCCCTATCTTTTCTATGTCCAA
60

GCTGTGCCCATCCAAAAAGTCCAAGATGACACCAAAACCCTCATCAAGACAATTGTCACC
120

AGGATCAATGACATTTCACACACGCAGTCAGTCTCCTCCAAACAGAAAGTCACCGGTTTG
180

GACTTCATTCCTGGGCTCCACCCCATCCTGACCCTGTCCAAGATGGACCAGACACTGGCA
240

GTCTACCAACAGATCCTCACATCGATGCCTTCCAGAAACGTGATCCAAATATCCAACGAC
300

CTGGAGAACCTCCGGGATCTTCTTCACGTGCTGGCCTTCTCTAAGAGCTGCCACTTGCCC
360

TGGGCCAGTGGCCTGGAGACCTTGGACAGCCTGGGGGGTGTCCTCGAGGCTTCAGGCTAC
420

TCCACAGAGGTGGTGGCCCTGAGCAGGCTGCAGGGGTCTCTGCAGGACATGCTGTGGCAG
480

CTGGACCTCAGCCCCGGGTGCGAGCCCAAATCGGCCGACAAAACTCACACATGCCCACCG
540

TGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAG
600

GACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
660

GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG
720

ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTC
780

CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTC
840

CCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTG
900

TACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCG
960

The cDNA encoding the full length human leptin (nucleotides 1-501) is joined at the 3' end to the 5' end of the hinge-CH2-CH3 region of the IgG1 cDNA (nucleotides 508-1203). The two amino acid linker between the two parts of the fusion is encoded by the nucleotide sequence GGTACC (502-507). See Table 1.

The encoded protein sequence of the leptin/IgG1(GT) chimera is given in Table 2. Leptin 1-1 (numbering as Y. Zhang, R. Proenca, M. Maffei, M. Barone, L. Leopold & J. Friedman. Nature 372:425-432), followed by the GT linker (168-169) and IgG1 H-CH2-CH3 170-401.

The gene coding for the human IgG1 contains a number of nucleotide substitutions compared to the IgG1 molecule described by Ellison J.W., Berson B.J. and Hood L.E., Nucleic Acids Research vol 10 No. 13 pp4071-4079, 1982. The IgG1 nucleotides which differ from the Ellison J.W. et al published sequence and the resulting amino acid substitutions are as follows (nucleotide numbering as in table 1)

nucleotide 519 is "G" in this variant compared to "T" in the Ellison et al sequence (silent mutation)

nucleotides 520-522 are "GCC" in this variant compared to "TGT" in the Ellison et al sequence (resulting in substitution of Ala for Cys in this variant, amino acid 174 in table 2)

nucleotide 759 is "T" in this variant compared to "G" in the Ellison et al sequence (silent mutation)

nucleotide 924 is "G" in this variant compared to "T" in the Ellison et al sequence (resulting in substitution of Glu for Asp in this variant, amino acid 308 in table2)

nucleotide 928 is "A" in this variant compared to "C" in the Ellison et al sequence (resulting in substitution of Met for Val in this variant, amino acid 310 in table 2)

nucleotide 1077 is "T" in this variant compared to "C" in the Ellison et al sequence (silent mutation)

nucleotide 1197 is "G" in this variant compared to "A" in the Ellison et al sequence (silent mutation)

The fusion protein was expressed transiently in Cos1 cells using the pCDN vector system, as described in International Patent Application Publication number WO 96/04388. The mature protein was exported from the cells into the culture medium and was detected by anti-leptin antibody. It was shown to to have a size consistent with the predicted structure by Western blotting analysis under both reducing and nonreducing conditions.

Table 7. DNA sequence of ob/IgG1'GT' chimera , 1203bp

```
ATGCATTGGGGAACCCTGTGCGGATTCTTGTGGCTTTGGCCCTATCTTTTCTATGTCCAA
                                                              60
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AAG
1203

Table 8. Amino acid sequence of leptin/IgG1 'GT' chimera, 401aa

1 MHWGTLCGFL WLWPYLFYVQ AVPIQKVQDD TKTLIKTIVT RINDISHTQS

51 VSSKQKVTGL DFIPGLHPIL TLSKMDQTLA VYQQILTSMP SRNVIQISND

101 LENLRDLLHV LAFSKSCHLP WASGLETLDS LGGVLEASGY STEVVALSRL

151 QGSLQDMLWQ LDLSPGCGTE PKSADKTHTC PPCPAPELLG GPSVFLFPPK

201 PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY

251 NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP

301 QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP

351 VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG

401 K

iii) culturing said transformed host cell under conditions permitting expression of said DNA polymer to produce said chimera; and

iv) recovering said chimera.

12. A DNA polymer comprising a nucleotide sequence that encodes a chimera according to any one of claims 1 to 8.

13. A vector which comprises a DNA polymer according to claim 12.

14. A host cell transformed or transfected with a DNA polymer according to claim 12 or a vector according to claim13.

15. A pharmaceutical composition comprising a chimera as claimed in claim 1 and a pharmaceutically acceptable carrier.

16. A chimera according to claim 1, for use as an active therapeutic substance.

17. A chimera according to claim 1, for use in the treatment of obesity or diseases associated with obesity.

18. A method for the treatment of obesity or diseases associated with in human or non-human mammal, which method comprises administering to the sufferer an effective, non-toxic amount of a chimera as claimed in claim 1.

19. A chimera as claimed in claim 1, for use in the cosmetic treatment of human or non-human mammals.

20. A method for the cosmetic treatment of a human or non-human mammal, which treatment comprises administering an effective, non-toxic amount of a compound of the invention to a human or non-human mammal in need thereof.